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RESEARCH ARTICLE
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A PROSPECTIVE RANDOMIZED STUDY ON RAISE OF LIVER ENZYMES OF SODIUM VALPROATE AND LEVETIRACETAM IN CHILDHOOD GENERALIZED EPILEPSY IN A TERTIARY CARE HOSPITAL.

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ABSTRACT

Background: Sodium valproate and levetiracetam are widely prescribed for childhood generalized epilepsy. Sodium valproate is known to cause hepatic enzyme elevation, whereas levetiracetam's effect on liver function is less documented. Monitoring liver enzymes is essential to ensure drug safety in pediatric patients.**Methods:** This prospective, randomized study was conducted in the Department of Pediatrics, [GGH,Kadapa], over 3 months. A total of 100 children aged 2–14 years with newly diagnosed generalized epilepsy were randomly assigned to receive sodium valproate (n=50) or levetiracetam (n=50). Baseline liver function tests (LFTs) were performed before therapy initiation and repeated at 1 and 3 months. Primary outcome measures included changes in serum alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP) levels. Clinically significant elevation was defined as >2× the upper limit of normal.**Results:** By the 3-month follow-up, mean ALT and AST levels in the sodium valproate group had increased significantly from baseline ($p < 0.05$), with clinically significant elevation in 14% of patients. The levetiracetam group showed minimal, non-significant changes, with only 2% exhibiting mild elevations. No patient developed acute liver failure or required discontinuation due to hepatotoxicity.**Conclusion:** Sodium valproate is associated with a higher frequency of liver enzyme elevation compared to levetiracetam in children with generalized epilepsy. Regular LFT monitoring is strongly recommended for patients on sodium valproate, whereas levetiracetam may offer a safer hepatic profile in this age group.

KEYWORDS: Sodium valproate, Levetiracetam, Liver enzymes, Childhood epilepsy, Hepatotoxicity, Randomized study.

INTRODUCTION

Epilepsy is one of the most common chronic neurological disorders in childhood, affecting approximately 0.5–1% of the pediatric population worldwide. Generalized epilepsy accounts for a significant proportion of these cases and requires long-term antiepileptic drug (AED) therapy to control seizures and improve quality of life[1].

Sodium valproate is a broad-spectrum AED widely used in children due to its efficacy in controlling generalized seizures. However, it is associated with doserelated and idiosyncratic adverse effects, including hepatotoxicity. Hepatic dysfunction induced by sodium valproate may manifest as asymptomatic liver enzyme elevation or, rarely, severe liver injury, particularly in younger children and those receiving polytherapy[2,3]. The mechanism is thought to involve mitochondrial toxicity and inhibition of fatty acid metabolism[4].

Levetiracetam is a newer broad-spectrum AED with a distinct mechanism of action—binding to synaptic vesicle protein 2A—and a favorable safety profile. It undergoes minimal hepatic metabolism, being predominantly excreted unchanged in urine, and is thus less likely to cause hepatotoxicity[5,6]. However, data regarding its long-term effects on liver enzymes in the pediatric population remain limited.

Given the potential hepatic risks of sodium valproate and the limited evidence regarding levetiracetam's hepatic safety in children, comparative studies are important for guiding clinical decisions. This study aims to prospectively evaluate and compare the incidence and degree of liver enzyme elevation in children with generalized epilepsy receiving sodium valproate or levetiracetam in a tertiary care setting.

MATERIALS AND METHODS:

This was a prospective, randomized, parallel-group study conducted in the Department of Pediatrics at GGH, Kadapa over a period of 3 months. A total of 100 children aged 2–14 years with newly diagnosed generalized epilepsy were enrolled. Diagnosis was based on clinical history, neurological examination, and electroencephalography (EEG) findings, in accordance with the International League Against Epilepsy (ILAE) classification.Inclusion criteria includes Children aged 2–14 years with newly diagnosed generalized epilepsy ,Normal baseline liver function tests (LFTs),No prior antiepileptic drug therapy. Exclusion criteria includes children with Pre-existing liver disease or abnormal baseline LFTs , History of metabolic or mitochondrial disorders, Use of hepatotoxic medications in the preceding 3 months ,Known hypersensitivity to study drugs. A total of 100 children will be randomly assigned to two groups A and B of 50 each. Group A will receive sodium Valproate 15-30mg/kg/day is given in two divided doses, Group B will receive Levetiracetam 10-30mg/kg/day in two divided doses and the dose will be titrated based on individual patient needs. Liver Function Tests for raised liver enzyme levels like ALT, AST, ALP will be measured at first visit, 1 and 3months.

Ethical Committee Permission:

The study was approved by the Institutional Ethics Committee. Written informed consent was obtained from the parents or legal guardians of all participants prior to enrollment.

Statistical Analysis:

Data were analyzed using SPSS version 26.Categorical variables were expressed as percentages and compared using Chi-square test. Continuous variables were expressed as mean ± standard deviation and compared using Student's t-test. A p-value < 0.005 was considered statistically significant.

RESULTS:

A total of 100 children (mean age 8.1 ± 3.4 years; 58 males, 42 females) were randomized equally into sodium valproate (n = 50) and levetiracetam (n = 50) groups. Baseline demographic and clinical characteristics were comparable between groups ($p > 0.05$).

Primary outcome

By the 3-month follow-up, the sodium valproate group showed a significant increase in mean ALT and AST levels compared to baseline, whereas the levetiracetam group showed minimal, non-significant changes.

Table 1. Comparison of liver enzyme changes between sodium valproate and levetiracetam groups

Time point	Sodium valproate (n = 50) Mean ± SD	Levetiracetam (n = 50) Parameter Mean ± SD	pvalue
ALT (U/L) Baseline	25.8 ± 6.2	26.1 ± 5.9	0.81
1 month	34.5 ± 8.1	27.2 ± 6.1	<0.005
3 months	38.9 ± 9.5	28.1 ± 6.4	<0.005
AST (U/L) Baseline	26.4 ± 6.5	25.9 ± 6.3	0.74
1 month	33.2 ± 7.9	26.7 ± 6.4	<0.005
3 months	37.8 ± 9.1	27.1 ± 6.6	<0.005
ALP (U/L) Baseline	180.4 ± 32.5	178.7 ± 33.1	0.76
1 month	184.2 ± 34.6	179.1 ± 33.8	0.43
3 months	186.5 ± 35.1	179.4 ± 33.7	0.37

Secondary outcomes

- **Clinically significant elevation (>2× ULN):** 6 patients (12%) in the sodium valproate group vs 1 patient (2%) in the levetiracetam group ($p < 0.005$).
- **Symptomatic hepatotoxicity:** Mild symptoms (fatigue, abdominal discomfort) in 3 patients in the sodium valproate group; none in levetiracetam group.
- No cases of acute liver failure were reported.

DISCUSSION

In this prospective randomized study, sodium valproate was associated with a significantly higher rise in liver enzyme levels (ALT and AST) compared to levetiracetam in children with newly diagnosed generalized epilepsy, with differences evident as early as 1 month and persisting at 3 months ($p < 0.005$). These findings are consistent with earlier studies reporting that sodium valproate can cause asymptomatic transaminase elevations in 5–15% of pediatric patients, particularly during the initial months of therapy.The hepatotoxic potential of sodium valproate is well recognized. Mechanistically, it is attributed to mitochondrial dysfunction, impaired βoxidation of fatty acids, and oxidative stress in hepatocytes. Our results reinforce the need for routine liver function monitoring, especially within the first 3 months of treatment.

Levetiracetam, in contrast, showed no significant alterations in liver enzyme levels. This is in agreement with prior studies demonstrating its minimal hepatic metabolism and predominant renal excretion. The low incidence of liver enzyme elevation in our study (2%) suggests a favorable hepatic safety profile, making levetiracetam a safer alternative in patients at risk for hepatic dysfunction.

Clinically significant enzyme elevation (>2× ULN) occurred in 12% of sodium valproate patients versus 2% of levetiracetam patients ($p < 0.005$). Although no cases of acute liver failure were observed, three children in the sodium valproate group developed mild symptoms, underscoring the importance of early detection and management.

The strengths of this study include its randomized design, well-matched baseline characteristics, and prospective monitoring at multiple time points. Limitations include a relatively short follow-up period of 3 months and a single-center design, which may limit generalizability. Longer-term studies with larger sample sizes are warranted to confirm these findings and explore potential risk factors for hepatotoxicity.

CONCLUSION

Sodium valproate therapy in children with generalized epilepsy is associated with a significantly higher incidence and magnitude of liver enzyme elevation compared to levetiracetam ($p < 0.005$). Given the potential risk of hepatotoxicity, baseline and periodic liver function monitoring are strongly recommended during sodium valproate therapy. Levetiracetam demonstrated a safer hepatic profile in this study and may be preferred in patients with preexisting liver risk factors or those intolerant to sodium valproate.

REFERENCES

1. Wirrell EC. Predicting pharmacoresistance in pediatric epilepsy. Epilepsia. 2013;54 Suppl 2:19–22.
2. Bryant AE, Dreifuss FE. Valproic acid hepatic fatalities. III. U.S. experience since 1986. Neurology. 1996;46(2):465–469.
3. Dreifuss FE, Langer DH. Hepatic considerations in the use of valproic acid. Epilepsia. 1989;30 Suppl 2:S17–S22.
4. Tong V, Teng XW, Chang TKH, Abbott FS. Valproic acid I: Time course of lipid peroxidation biomarkers, liver toxicity, and valproic acid metabolite levels in rats. Toxicol Sci. 2005;86(2):427–435.
5. Lyseng-Williamson KA. Levetiracetam: A review of its use in epilepsy. Drugs. 2011;71(4):489–514.
6. Patsalos PN. Clinical pharmacokinetics of levetiracetam. Clin Pharmacokinet. 2004;43(11):707–724.